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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/211,794	12/15/1998	AMY ARROW	8824-016	9449

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/211,794	ARROW ET AL.
Examiner	**Art Unit**
Mary M. Schmidt	1635

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Aug. 30, 2002, has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of cleaving an RNA in a cell in cell culture (*in vitro*), does not reasonably provide enablement for methods of cleaving an RNA in a cell in a whole organism (*in vivo*). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 18 is drawn to a method of specifically cleaving an RNA in a cell containing RNase H which comprises administering an effective amount of an oligonucleotide complementary to the RNA. The claimed method does not specify that the cells are in cell

culture, as such the claim reads on administration of the claimed antisense to cells in a whole organism.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical

translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who

teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by

the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (U.S. Patent, 5,576,208; IDS Reference AA-1), Milligan et al. (J. Of Medicinal Chemistry, vol. 36, no. 14, pages 1923-1937, 1993), and Matulic-Adamic et al. (U.S. Patent 5,998,203).

Note that U.S. Patent 5,998,203 was not available as prior art at the time the parent application, U.S. Application no. 08/754,580, was examined and issued.

Claim 1 is drawn to any chimeric antisense oligonucleotide comprising a 5'terminus, a 3'terminus and from 11-59 5' to 3' linked nucleotides which contiguously hybridize to a specific RNA and which are independently selected from a group including 2'-modified phosphodiester nucleotides and 2'-modified P-alkyloxyphosphotriester nucleotides; and wherein said 11-59 5' to 3'-linked nucleotides are divided by an Rnase H-activating region which contiguously hybridizes to the specific RNA and comprises between 3 and 10 contiguous phosphorothioate-linked deoxyribonucleotides, and wherein the 3'-terminus of said oligonucleotide is from the group consisting of: an inverted deoxyribonucleotide, a contiguous stretch of 1 to 3 2'-modified ribonucleotides, a biotin group, and a P-alkyloxyphosphodiester nucleotide, and wherein the 5' terminus of said oligonucleotide is drawn from the group consisting of and inverted deoxyribonucleotide, a contiguous stretch of 1 to 3 phophorothioate2'-modified ribonucleotides, a biotin group, and a P-alkyloxyphophodiester nucleotide.

Claim 2 specifies that the 3'-terminus is not blocked by a 3'-3' phosphorothioate linked nucleotide. Claim 3 specifies that the 3' terminus is blocked by a moiety comprising a 3'-3' phosphorothioate linked nucleotide. Claim 4 specifies that the 3' terminus is blocked by a moiety comprising a 3'-3' phosphodiester linked nucleotide. Claim 5 specifies that the 3' most 5'-3' internucleotide linkage is a phosphorothioate linkage or a P-ethoxyphosphotriester linkage. Claim 6 specifies that the 5' most 5'-3' internucleotide linkage is a phosphorothioate linkage or a P-ethoxyphosphotriester linkage. Claim 7 specifies that the 3' terminal nucleoside and the 5' most nucleoside are 2'-modified nucleotides. Claim 8 specifies that the 5' most 5'-3'

internucleotide linkage is a phosphorothioate linkage or a P-ethoxyphosphotriester linkage. Claim 9 specifies that the two 5' most 5'-3' internucleotide linkages are independently either a phosphorothioate linkage or a P-ethoxyphosphotriester linkage. Claim 10 specifies that all phosphothioate linkages are contiguous with the 3' most 5'-3' internucleotide linkage. Claim 11 specifies that the 2'-modified nucleotide is a 2'-methoxy or 2'-fluoro nucleotide. Claim 12 specifies that the oligonucleotide comprises at least 13 2'-methoxy phosphodiester nucleotides. Claim 13 specifies that the oligonucleotide has between 15 and 50 nucleotides. Claim 14 specifies that the oligonucleotide comprises at least 8 2'-methoxy phosphodiester nucleotides. Claim 15 specifies that the oligo comprises at least 13 2'-methoxy phophodiester nucleotides. Claim 16 specifies that the oligonucleotide 2'-modified nucleotides are selected from the group consisting of 2'-fluoro and 2'-methoxy nucleotides. Claim 17 specifies that there are no 2'-modified phosphorothioate nucleotides.

Claim 18 is a methods of cleaving RNA in a cell containing RNase H which comprises administering an effective amount of an oligonucleotide complementary to the RNA. Claim 18 is included in the instant rejection for the breath of administering the claimed oligonucleotides to cells in cell culture.

Claim 19 is drawn to a chimeric antisense oligonucleotide comprising a) an Rnase H activation region which contiguously hybridizes to a specific RNA and which has between 5 and 10 contiguous deoxyphosphorothioate nucleotides; b) between 4 and 59 contiguous 5'-3' linked 2'-methoxyribonucleotides which contiguously hybridize to the specific RNA; and c) an

exonuclease blocking group present at the 3' end, the 5' end, or both the 3 and 5' ends of the oligonucleotide drawn from the group consisting of : a non-5'-3' phosphodiester-linked nucleotide, from 1 to 3 contiguous 5'-3' linked modified nucleotides, and a non-nucleotide chemical blocking group.

Monia et al. (U.S. Patent 5,576,208; IDS reference AA-1) are relied upon to teach by way of example design of several different kinds of antisense oligonucleotides targeting the Ras gene. They teach in figure 5A, oligos having from 5 to25 nucleic acids in length. They teach in col. 16, that the addition of 2'-O-methyl deoxy "gaps" to their antisense oligonucleotides to "direct Rnase H cleavage of a complementary RNA... in vitro... as described in Example 8. As shown in FIG. 10, no cleavage was observed with the fully modified 2'-O-methyl oligonucleotide or one containing a single deoxy residue. Oligonucleotides with a deoxy length of three, four, five, seven or nine were able to direct Rnase H cleavage. Deoxy gaps of five, seven or nine are preferred and gaps of seven or nine are most preferred.... The beneficial properties of enhanced target affinity conferred by 2'-O-methyl modifications can be exploited for antisense inhibition provided these compounds are equipped with Rnase H-sensitive deoxy gaps of the appropriate length... As shown in FIG 11, chimeric 2'-O-methyl oligonucleotides containing deoxy gaps of five or more residues inhibited H-ras gene expression. These compounds displayed activities greater than that of the full deoxy parent compound." (Col. 16, lines 5-30) In col. 16, line 66, through col. 17, line 4, they further taught that with asymmetrical deoxy gaps: "it is not necessary

that the deoxy gap be in the center of the chimeric molecule. It was found that chimeric molecules having the nucleotides of the region at one end modified at the 2' position to enhance binding and the remainder of the molecule unmodified (2'deoxy) can still inhibit ras expression." In col. 4, lines 6-40, they also taught the motivation for making chimeric antisense oligonucleotides: "chimeric oligonucleotides contain two or more chemically distinct regions.... These oligonucleotides typically contain a region of modified nucleotides that confer one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased biding affinity for the RNA target) and an unmodified region that retains the ability to direct Rnase H cleavage. This approach has been employed for a variety of backbone modifications, most commonly methylphosphonates, which alone are not substrates for RNAse H." In col. 4, lines 41-46, they state that "[i]t is presently preferred that increased binding affinity is conveyed by modification of at least one nucleotide at the 2'position of the sugar, most preferably comprising a 2'-O-allyl, 2'-O-alkylamino or 2'-fluoro modification." Their 2'-O-modified bases have phosphodiester linkages. They further teach in col. 4 lines 41-50 the motivation for providing a "cap" at the 3' and/or 5' end of the antisense "in order to provide stability against exonucleases which permitting RNAse H activation." They do not specifically state an inverted deoxyribonucleotide as either a 3' terminus or a 5' terminus. They do not teach use of any P-alkyloxyphosphotriester nucleotides.

Milligan et al. is further relied upon to teach the design of antisense oligonucleotides having different kinds of backbones, including alkyl phosphotriester (see Table 1, page 1923),

but not P-alkyloxyphosphotriester or P-ethoxyphosphotirester as instantly claimed. In Table 1 they teach that alkyl phosphotriester does not activate RNAse H (and could not be used in an Rnase H degradation region), but is resistant to nucleases. They teach on page 1925, col. 2 that "[t]he naturally occurring phosphodiester linkages in ODNs are susceptible to degradation by endogenously occurring cellular nucleases, while phosphorothioate and methylphosphonate linkages are highly resistant to nuclease degradation. Phosphodiester ODNs are known to be rapidly degraded in serum containing tissue culture media by 3'-exonuclease activity. Protection from degradation can be achieved by use of a "3'-end cap" strategy in which nuclease-resistant linages are substituted for phosphodiester linkages at the 3'-end of the ODN. Phosphoramidates, phosphorothioates, and methylphosphonate linkages all function adequately in this manner." They further teach the pitfalls of antisense in serum and cells as two-fold, degradation and lack of permeability to the inside of the cells. On page 1931, they further discuss modifications of the phosphodiester backbone "to impart stability and... allow for enhanced affinity and increased cellular permeation of ODNs." Included in their list of backbone modifications is use of a phosphotriester (figure 3, page 1931). They reference Marcus-Secura to teach use of alkyl phosphotriesters, but Marcus-Sekura does not further teach use of P-alkyloxyphosphotriester or P-ethoxyphosphotirester as instantly claimed (see page 1932, col. 1, line 21). For sugar modifications they also teach use of the 2'-O-methyl "to enhance resistance to degradation, compared with normal RNA, without compromising affinity." (Sentence bridging pages 1932 and 1933).

Matulic-Adamic et al. (U.S. Patent 5,998,203) is further relied upon to teach the specific use of 5'-and/or 3'-cap structures such as 5'-5'-inverted abasic moieties and 3'-3'-inverted abasic moieties (claim 1 of '203, col. 37). They teach that such modifications may be used on both RNA and single stranded DNA (col. 2, lines 44-58) to "protect the enzymatic nucleic acids from exonuclease degradation. Resistance to exonuclease degradation can increase the half-life of these nucleic acids inside a cell and improve the overall effectiveness of the enzymatic nucleic acids. These terminal modifications can also be used to facilitate efficient uptake of enzymatic nucleic acids by cells, transport and localization of enzymatic nucleic acids within a cell, and help achieve an overall improvement in the efficacy."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a chimeric antisense oligonucleotide from 11-59 bases having the nucleic acid composition of a 5' and 3' terminus, and 2'-O-modified phosphodiester nucleotides since both Monia et al. and Milligan et al. taught use of 2'-O-modified phosphodiester nucleotides and a 5' and 3' cap region. It would have been further obvious to make the claimed antisense with an RNAse H-activating region of the size specified by Monia et al. It would have been further obvious to optionally use the 5' and 3' inverted bases taught by Matulic-Adamic et al. for exonuclease degradation resistance. It would have been further obvious to make the antisense with phosphorothioates at the 5', 3' or other regions as taught by Monia et al. and

Milligan et al. It would have been further obvious to use said oligonucleotides in cells in cell culture as taught by Monia et al. and Milligan et al.

One of ordinary skill in the art would have been motivated to make an antisense oligonucleotide having the claimed 5' and 3' regions, the RNase activating region, and additional modifications such as 2'-O-methyl modifications and phosphorothioate modifications since Monia et al. taught the improved benefits of having "gapped" oligonucleotides with 2'-O-alkyl nucleotides (including 2'-O-methyl and 2'-O-allyl nucleotides) of a length of 7 nucleotides, a length preferred for effective RNAse H activation, Matulic-Adamic et al. taught the improved benefits of an optional 5' and/or 3' cap composed of 5'-5'-inverted abasic moieties and 3'-3'-inverted abasic moieties to increase the half-life of the oligonucleotide administered to cells in culture.

One of ordinary skill in the art would have had an expectation of success to make an antisense oligonucleotide to a desired target gene having the combinations of the claimed nucleic acid modifications since all of the claimed nucleic acid modifications were well-known in the art of antisense as taught by Monia et al., Matulic-Adamic et al., and Milligan et al. for improved stability of the antisense oligonucleotides to unwanted degradation prior to binding the target RNA molecule, and further improved degradation of the antisense/target RNA nucleic acid hybrid by RNAse H. One of skill in the art would have had an expectation of success to use the antisense having the claimed modifications and further having specific base sequences complementary to a desired gene target sequence (specifically to a region found to be open and

available to antisense binding via Watson-Crick base interactions) for administration to a cell in cell culture expressing the target gene, for antisense inhibition of the target gene.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
November 18, 2002

JOHN [illegible]
SUPERVISORY [illegible] EXAMINER
TECHNOLOGY [illegible]00